DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Meeting Minutes

Meeting Date: June 1, 2000 **Time**: 2:00 p.m. to 3:00 p.m. **Location**: WOC2 I

Re: Docket No. 90N-0056; Final Rule on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition

External participant: Health Industry Manufacturers Association (HIMA)

Type of meeting: Discussion of Final Rule Provisions

Meeting Chair: Jane Axelrad **External participant lead**: Marcia Marconi

Meeting Recorder: Leanne Cusumano

FDA Attendees, titles and offices:

Jane Axelrad	Associate Director for Policy, Center for Drug Evaluation & Research (CDER) (HFD-5)
Yuan-Yuan Chiu	Director, Office of New Drug Chemistry (ONDC), CDER (HFD-800)
Eric Colman	Medical Officer, Metabolic & Endocrine Drug Products, CDER (HFD-510)
Leanne Cusumano	Regulatory Counsel, CDER (HFD-7)
Chuck Hoiberg	Deputy Director, ONDC, CDER (HFD-800)
David Lewis	Chemist, Division of New Drug Chemistry II, CDER (HFD-510)
Dave Read	Supervisory Regulatory Counsel, CDER (HFD-7)
Duu-Gong Wu	Chemist, Division of New Drug Chemistry II, CDER (HFD-510)

External constituent and titles:

Jose Joseph	Abbott Laboratories, R&D
Russell Madsen	PDA
Karen Malik	Baxter Healthcare Corporation
Marcia Marconi	Baxter Healthcare Corporation
Frank Pokrop	Abbott Laboratories
Lisa Skeens	Baxter Healthcare Corporation
John Spoden	B. Braun Medical, Inc.
Marlene Tandy	Director, Technical & Regulatory Affairs & Associate General Counsel, HIMA
Martin VanTrieste	Abbott Laboratories, QA

90N-0056

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Meeting Objectives: Determine Agency acceptability of industry proposals regarding implementation of the aluminum final rule.

Discussion Points:

1. Inadequate time for final rule implementation.
   - HIMA proposes 1 year (01/26/2001) to get warning on all packages, 2 years (01/26/2002) to comply with the remainder of the rule, except 3 years (01/26/2003) for those LVPs requiring reformulation and/or repackaging.
   - HIMA states that additional time is necessary for moving methods validation from research and development to production, to order and install equipment, and to reduce levels in raw materials

2. Insufficient space on immediate container label of small volume parenterals (SVPs).
   - HIMA requests an exemption for small containers.

3. Large volume parenterals (LVPs) that will not meet the 25 ug/L limit.
   - HIMA states that most LVPs fall in the 50 ug/L or less range, and that not all can currently meet the 25 ug/L limit.
   - Lipid emulsions in glass are generally meeting the 25 ug/L limit.
   - Amino acids, particularly those with phosphates, are probably not meeting the limit, and it may be difficult for them to meet the limit at all.

4. Release data required for submission may not be available for low production products.
   - HIMA proposes submittal of historical batch release or stability data until several batches produced.

5. Labeling clarification for SVPs and pharmacy bulk packages (PBPs).
   - HIMA requests that FDA permit labeling for those products with less than 25 ug/L to carry labeling that simply states "contains less than 25 ug/L" rather than requiring such products to carry an exact amount.
   - HIMA states that many PBPs and some SVPs already fall below the 25 ug/L level.
   - This would avoid unnecessary and clinically irrelevant labeling changes.

6. Uniform approach to aluminum testing on stability so that all products measure stability at the same time.
   - HIMA proposes time zero and annually thereafter.

7. Clarification that final rule applies only to LVP, SVP, and PBP DRUGS used in total parenteral nutrition (TPN) and not to devices.
   - HIMA stated that some people within the agency misunderstand the scope of the rule.

Decisions (agreements) reached:

1. HIMA's proposal #4 to submit historical batch release or stability data until several batches produced is consistent with the final rule as it exists.

2. HIMA's proposal #6 to test stability at time zero and annually thereafter is consistent with the final rule as it exists.

3. HIMA is correct in stating that the final rule applies only to LVP, SVP, and PBP drugs used in TPN (#7).

Action Items:

1. HIMA will provide to FDA its best estimate of whether there are any LVPs that will never be able to meet the 25 ug/L limit, and if so which ones.

2. FDA will contact HIMA within three weeks, or on or before June 22, 2000, to advise them as to whether it will take no action, issue guidance, or issue a proposed rule on the following:
   - whether a change in the implementation date is appropriate (#1 and #3);
   - whether 21 CFR 201.110 permits a small package exemption (#2);
   - whether SVPs with less than 25 ug/L of aluminum may be labeled with a statement that they contain less that 25 ug/L of aluminum rather than an exact aluminum level (#4).

3. FDA will provide minutes to Marlene Tandy at HIMA as soon as possible, but no later than June 29, 2000, in accordance with CDER's internal policies.

Signature, minutes preparer:

Concurrence Chair (or designated signatory): Jana A. Axelrad

Attachment/Handouts:
HIMA Slides

cc:
Docket No. 90N-0056
Marlene Tandy, HIMA
JAxelrad, HFD-5
DRead, HFD-7
LCusumano, HFD-7
YChiu, HFD-800
CHoiberg, HFD-800
EColman, HFD-510
DWu, HFD-510
DLewis, HFD-510

Final Rule on Aluminum in Large and Small Volume Parenterals Used in Total Parenteral Nutrition

HIMA LVP Task Force Meeting
with FDA Representatives
May 18, 2000

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Objective/Agenda

OBJECTIVE:

- Determine Agency acceptability of industry proposals regarding implementation of the Aluminum Final Rule

AGENDA:

- Inadequate Time for Final Rule Implementation
- Insufficient Space on Immediate Container Labels of SVPs
- LVP Products that Will Not Meet the Required Aluminum Limit
- Release Data for Aluminum Required for Submission
- Labeling Clarification for SVPs and PBPs
- Agreement on Uniform Approach to Aluminum Testing on Stability
- Clarification of the Scope of the Final Rule
- Discussion

Issue 1: Inadequate Time for Final Rule Implementation

- Final Rule requires implementation of all aspects of final rule within one year of publication (1/26/00)
- Numerous technical, manufacturing, supplier and regulatory issues present unusual hurdles for industry to comply with this implementation date
- Number of products and applications affected is significant
  - More than 500 products and 85 NDAs impacted for task force firms

Industry Proposal: Inadequate Time for Final Rule Implementation

- Industry will implement the required aluminum warning statement in the "Warnings" section of the PI for all LVPs, SVPs and PBPs within 1 year of final rule publication
- Industry will implement all other provisions of the final rule within 2 years of final rule publication
  - Modify LVP package inserts to state that the drug product contains no more than 25 µg/L of aluminum. This will be contained in the "Precautions" section.
  - Modify SVP and PBP immediate container labels to contain the statement "Contains no more than _ µg/L of aluminum"
  - Submit "CBE" Supplements to affected NDAs/ANDAs incorporating labeling changes, methods validation information, and batch data

Issue 2: Insufficient Space on Immediate Container Labels of SVPs

- It is not physically possible to add a legible aluminum statement on SVPs with restricted space on immediate containers
  - Many of these products already have labeling exemptions, and we request a variance to the final rule for this circumstance as well

Industry Proposal:

- The relevant aluminum statement may be located on the multi-container package for SVP products with restricted label space on the immediate container
  - For example, on the folded box which contains several ampoules

Issue 3: LVP Products that Will Not Meet the Required Aluminum Limit

- Final Rule requires LVP drug products to contain no more than 25 µg aluminum.
- Aluminum levels can be lowered by screening raw materials and shortening expirations. A limited number of products will still be above 25 µg aluminum limit.
- Reformulating and changing immediate container materials will likely bring these products into acceptable limits, but this will take at least 2-3 years.
  - Development activities include studies, sterilization and stability studies. Prior FDA approval will also be required.
- If these products need to be withdrawn on 1/26/01, there may be an adverse impact on public health and safety because there may be no alternative products available

Industry Proposal: LVP Products that Will Not Meet the Required Aluminum Limit

- Industry requests a variance to the final rule for these particular products
- Specified LVP products not able to meet 25 µg/L aluminum limit without reformulation/repackaging will meet the elements of the final rule required for SVPs and PBPs for an interim period not to exceed 3 years after publication of the final rule
  - This will include modification of the LVP immediate container labels to contain the statement "Contains no more than _ µg/L of aluminum"
- This variation will allow these specific drug products to remain on the market until they can be modified, and in the interim will notify clinicians of the aluminum content so they can make informed decisions for their patients

Issue 4: Release Data for Aluminum Required for Submission

- Final rule requires release data for several batches be included in the CBE supplements
- Industry requests that historical batch release data or stability data be sufficient for submission purposes as this would meet the intent of the requirement for batch release data
  - This is particularly important for product codes that are extremely low in production volume and therefore only manufactured infrequently

Industry Proposal:

- Historical batch release or stability data for several batches should be sufficient for CBE purposes
- A commitment could be included in the CBE submission to submit batch release data for aluminum for several batches as it becomes available

Issue 5: Labeling Clarification for SVPs and PBPs

- Final Rule requires the max level of aluminum present at expiry be stated on the immediate container of all SVPs and PBPs
- For SVPs and PBPs that will have a max level of aluminum below 25 µg/L industry would like the option to label the products: *"Contains no more than 25 µg/L of aluminum"*
  - This would significantly simplify process of determining max levels at expiry for these products that have very low levels
  - Likely to prevent unmeaningful labeling revisions in future years
  - Max level of 25 µg/L of aluminum was determined to be suitable for LVPs and therefore should be acceptable for SVPs as well. Also, it may not be clinically relevant whether a product is labeled with a maximum of 15 µg/L or 25 µg/L of aluminum

Industry Proposal: Labeling Clarification for SVPs and PBPs

- Industry should have the option to label the immediate container of SVPs and PBPs with the statement *"Contains no more than 25 µg/L of aluminum"* if the maximum level of aluminum at expiry for the drug product will be less than 25 µg/L
- A specific number derived from the three options outlined in the final rule should not be required

Issue 6: Agreement of Uniform Approach to Aluminum Testing on Stability

- Products impacted by the final rule will require aluminum testing on stability.
- Industry requests that FDA agree to common stability testing intervals for aluminum testing

Industry Proposal:

- Industry will conduct testing for aluminum at time zero, annually thereafter, and at expiry

Issue 7: Clarification of the Scope of the Final Rule

- Industry would like to confirm that the final rule applies only to LVPs, SVPs and PBPs used in TPN therapy
  - For example it does not apply to following LVPs:
    - 0.45 and 0.9% Sodium Chloride
    - 5% Dextrose
    - Lactated Ringers
    - Dextrose/Sodium Chloride/Potassium Chloride
    - Heparin
- We also want to confirm that it applies only to drug products, and not to solutions regulated as medical devices (i.e. flush syringes)